REMARKS

Claims 1, 5, 7-12, 20-22, 27 and 29-39 are now pending. Claims 6, 13-21 and 23-30 have been deleted without prejudice. Claims 31-39 have been added. Applicants acknowledge the Office's indication that claim 2 contains allowable subject matter. Claims 1, 3-5, 7, 12 and 22 have been amended to clarify the claim language. Support for the amendment to claims 1, 4 and 5 (in part), with respect to the coding region, is found in Figure 1 and also in the sequence listing. The references to the deposit information in the claims and also in the specification have been deleted. Claim 3 has been amended to delete the "selected from the group" language. The hybridization conditions set forth on page 15, last two lines have been incorporated into claim 4. Support is found for the amendment to claim 5, part a) and new claims 34-37, for example, on page 3, line 27; parts b) and d) and new claims 38-39 for example, on page 15, line 25; and part c) for example, on page 5, line 32. Further support for the amendment to claim 5 with respect to the kinase activity of the molecule is found for example, on page 8, lines 11-2, page 13, last paragraph, and page 14, lines 19-24. Claim 12 has been amended to indicate that the polypeptide is expressed by the nucleic acid molecule (defined in claims 1-5).

Support for new claim 31 is found on page 4, line 36. Support for new claims 32-33 is found in original claim 1.

Formal Matters

Formal drawings and a Request for Correction of Drawings are submitted herewith. Applicants respectfully request the Examiner to approve of the drawing changes in the request, upon which approval this objection may be withdrawn.

Also, as requested by the Office, Applicants have included a clean copy of the pending claims starting on page 7 of this Amendment.

Sequence Listing

The Specification has been amended to correct erroneous sequence identification numbers and include sequence identification numbers which were omitted at the time of filing.

The undersigned hereby states that the computer readable form copy (CRF copy) of the substitute Sequence Listing and the paper copy of the substitute Sequence Listing, submitted in accordance with 37 C.F.R. § 1.825(a) and (b), respectively, are the same and contain no new matter. Accordingly, entry of the substitute Sequence Listing into the above-captioned case is respectfully requested.

The Rejections Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 1, 3-6, 12 and 22 under 35 U.S.C. § 112, second paragraph is traversed and reconsideration is respectfully requested.

The specific nucleotides that comprise the coding region have been added into claims 1, 4 and 5, parts (a) and (b).

Claim 3 has been amended to delete reference to the deposit information, and to identify the sequence as SEQ ID NO:1.

Claims 4 and 22 have been amended to include the stringent hybridization conditions specified the specification.

Claim 7 has been amended to include the language kindly suggested by the Examiner.

Claim 12 has been amended to include that the polypeptide has been produced from the previously defined nucleotide sequence. The Office alleges that this claim omits an essential step, such as "how the polypeptide is produced or recovered once the host cell is cultured." The claim as originally written indicates that the polypeptide has been produced, and as amended indicates that the polypeptide comprises that which is expressed by the previously defined

nucleic acid molecule. The present specification does not disclose that the polypeptide must be recovered so it is respectfully submitted that this step is not necessary to define the method claim with definiteness. It is respectfully submitted that one may not necessarily want to recover the polypeptide, for example, if one wanted to alter the nature of the cell in which the polypeptide is produced. Thus, it is respectfully submitted that claim 12 is definite. Nonetheless, new claim 31 has been added and includes the step of isolating the polypeptide.

Accordingly, it is believed this basis for rejection may be withdrawn.

The Rejection Under 35 U.S.C. § 112, First Paragraph

Applicants gratefully acknowledge that claims 1-3 and claims 6-12 and 22, to the extent that claims 6-12 and 22 are directed only to the subject matter of claims 1-3, are properly viewed as in compliance with the requirements of 35 U.S.C. § 112, first paragraph. The rejection of claims 4 and 5 (and dependent claims 6-12 and 22) under 35 U.S.C. § 112, first paragraph (written description and enablement) is traversed and reconsideration is respectfully requested. Claim 6 has been deleted thus rendering this portion of the rejection moot.

With regard to the alleged lack of written description with respect to claim 4, directed to naturally occurring variants, the Office alleges that

> no disclosure of the function of the polypeptides encoded by the claimed polynucleotides has been provided [nor] ... disclosure of the critical structural elements required for eukaryotic initiation factor (eIF-2) kinase activity...[nor] disclosure of which structural elements (1) a variant ... should have to display the desired activity.

First, claim 4 has been amended to indicate that allelic variants that have kinase activity are included in the scope of the claim. In addition, claim 5, which is generally directed to homologs and fragments of SEQ ID NO:1, has been amended to define the nucleic acid molecule as encoding a polypeptide having kinase activity. Thus, the claims define the function of the encoded polypeptides, support for which is found in the present specification as described above

in contrast to the Office's suggestion that such disclosure has not been provided. Second, the specification provides guidance to one having ordinary skill in the art that describes which positions can be altered without loss of activity, in contrast to the Office's suggestion of the lack of critical structural elements required for *e.g.,* eIF-2 kinase activity. For instance Figure 2 shows the conserved regions of amino acids in two known EIF2 kinases with respect to the 14790 polypeptide. Further, Figure 7 shows the conserved regions in kinases as well as specifically for domains in the family of eucaryotic protein kinases (PFAM analysis), as well as for specific kinases (ProDom analysis). Therefore, it is respectfully submitted that a skilled person would understand which positions can be altered without loss of activity and therefore there is sufficient description of what the applicants described as their invention. Finally, it is respectfully submitted that a skilled artisan, armed with the information provided in the specification, would understand which structural elements a variant would have to display to achieve the desired kinase activity based on the above sequence comparisons.

The Office cites three references is support of its contention that a "sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide." The Bork (2000) reference was cited by the Office as alleging that "protein function is context dependent, and both molecular and cellular aspects must be considered." The Bork 2000 paper then cites the Bork 1998 paper as standing for this proposition, a copy of which is enclosed herewith. However, Bork 1998, a copy of which is enclosed herewith, does not stand for the unilateral proposition that protein function cannot be predicted using nucleic acid sequence analysis, therefore making the use of such functional predictions inappropriate or incorrect. Rather, Bork's "errors" consist of the "functional over- and under-predictions for a given database match." See Bork 1998, page 317,

first column. Bork therefore proposes the use of a variety of databases to ensure the maximal information regarding function(s) can be generated. See Bork 1998, page 315, first column (describing the searching of multiple databases as "an important complement to standard database searches" such as BLAST searches). In fact, Applicant has performed the multi-database analysis advocated by the Bork reference using some of the same databases. Specifically, Applicant analyzed the claimed nucleic acid sequence using the PFAM (Figures 7H-7M4), PROSITE (Figure 7E) databases, and SMART (Figures 7N-7R), all of which are recommended in Bork's paper, in addition to PRO DOM/BLAST database (Figures 7S-7A3). Thus, it is respectfully submitted that if errors were present in the BLAST searches, the other searches support and further confirm the function of the claimed nucleic acid sequence.

The Office cites Van deLoo and suggests that polypeptides of approximately 67% homology to a desaturase was a hydroxylase. Van deLoo tests the hypothesis that desaturase and hydroxylase share significant amino acid similarity. Also these enzymes both have an iron binding site, which is conserved in both enzymes. Such similarity and binding sites are not at issue here as the present claims are now directed to homologs, fragments or variants that retain kinase activity. Also, the claims were amended such that the claimed homologs are at least 85% homologous to SEQ ID NO:1 and at least 90% to nucleotides 63 to 4991 of SEQ ID NO:1. In addition, the claims define a nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence which is at least about 95% homologous to the amino acid sequence of SEQ ID NO:2. These molecules have much greater homology than the 67% homology between the desaturase and hydroxylase disclosed in Van deLoo.

Broun is cited to suggest that a few amino acid substitutions can convert a desaturase to a hydrolase. This may be true, but this reference represents an analysis of a particular alteration,

namely those of the *conserved* regions of desaturases, and is not descriptive of alterations in general, particularly when a skilled artisan would appreciate that only non-conserved regions must be altered to retain kinase activity as now claimed.

As the Office appears concerned that "[m]any functionally unrelated polypeptides are encompasses within the scope of these claims," it is respectfully submitted that the present claims that define fragments, homologs or variants that retain kinase activity overcome this concern. In addition, possession of a compound, and a written description thereof, do not require a description of every member of the genus described. The skilled artisan merely needs to recognize possession of applicants' concept of the invention as claimed. Accordingly, it is believed that the claims are sufficiently described in the specification.

With respect to the alleged lack of enablement of claims 4 and 5 (and dependent claims 6-8 and 22), the Office alleges that the "specification does not provide any information as to which structural elements are related to eIF-2 kinase activity nor is there disclosure of the structural elements within the polynucleotides as encompassed by the claims." As described above, the specification indeed has guidance of which amino acids are conserved. Further, Figure 7 shows how the structure, namely the polypeptide sequences, are related to its function as a kinase.

Furthermore, experimentation would be only routine to obtain variants or homologs since a substantial number of the claimed variants will retain kinase activity or have such a high degree of homology that they would remain active. The few that might lose activity by virtue of amino acid or nucleotide substitutions or deletions would not be difficult to eliminate by appropriate screens.

The attention of the Office is called to the decision in *Ex parte Mark*, 12 USPQ2d 1904 (Bd. Pat. App. & Int. 1989) which is quite similar to the facts here. In that case, claims were

drawn to muteins where at least one non-essential cysteine was replaced by another amino acid in *any* protein. The Examiner had rejected the claims on the basis that only three proteins were illustrated and the choice of the appropriate cysteine in other proteins was not taught. The Board held that the claims were fully supported as it was well within ordinary skill to test the limited number of possible muteins for retention of activity based on the amino acid sequence of any arbitrary protein. A copy of this decision is enclosed. Similarly, here, it is well within ordinary skill to make small amino acid or nucleotide changes and screen for kinase activity. Such screening is respectfully submitted not to be undue experimentation as suggested by the Office.

Accordingly, it is believed this basis for rejection may be withdrawn.

The Art Rejections

Applicants gratefully acknowledge that claims 1-4 and claims 7-12 and 22, to the extent that claims 7-12 and 22 are directed only to the subject matter of claims 1-4, are free from art. The rejection of claims 4-6 (and dependent claims 7-12 and 22) under 35 U.S.C. § 102 over Berlang and Duesterhoeft is traversed and reconsideration is respectfully requested. Claims 6 has been deleted thus rendering the rejection as to this claim moot.

The claims have been amended such that they do not encompass the subject matter of the cited references. Thus, this rejection may be properly withdrawn.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 381552000200.

Respectfully submitted,

Dated: January 13, 2003 By: _____

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please amend the paragraph on page 3, lines 26-38, as follows:

In one embodiment, a kinase encoding a nucleic acid molecule of the invention is at 75%, 77%, 80%, 82%, 85%, 87%, 90%, 92%, 95%, 97%, 98%, 99% or greater homology to a nucleotide sequence (e.g., to the entire length of the nucleotide sequence) including SEQ ID NO:1 or a complement thereof. [ ] In a preferred embodiment, the isolated nucleic acid molecule includes the nucleotide sequence shown SEQ ID NO:1 or a coding region of SEQ ID NO:1, or a complement thereof. In another embodiment, the nucleic acid molecule includes the 5' UTR and the coding region of SEQ ID NO:1. In yet another embodiment, the nucleic acid molecule includes the coding region of [SEQ ID NO:3] SEQ ID NO:1 and the 3' UTR of SEQ ID NO:1. In another preferred embodiment, the nucleic acid molecule has the nucleotide sequence shown in SEQ ID NO:1 or the coding region of SEQ ID NO:1. In another preferred embodiment, the nucleic acid molecule comprises a fragment of at least 4400 nucleotides of the nucleotide sequence of SEQ ID NO:1 or the coding region of SEQ ID NO:1, or a complement thereof.

Please amend the paragraph on page 7, lines 3-8, as follows:

Figures [7 a-n] 7 a-a3 comprise various regions of SEQ ID NO:2, as well as comparison sequences, [(SEQ ID NOS: 7-32)](SEQ ID NOS: 8-33), data generated to show PFAM cites, hydrophobicity/ hydrophilicity, and cysteine residues of the amino acid sequence of SEQ ID NO:2, as well as PSORT prediction of protein localization, signal peptide predictions, transmembrane segments predicted by MEMSAT, Prosite pattern matches, protein family/domain matches and ProDom matches of the amino acid sequence of SEQ ID NO:2.

Please amend the paragraph on page 7, lines 25-29, as follows:

Figures 1 a-k depict[s] the cDNA sequence and predicted amino acid sequence of human kinase. The nucleotide sequence corresponds to the 5525 nucleic acids of SEQ ID NO:1 which include nucleic acids 1-4950 of the coding region (SEQ ID NO:3), the 5' UTR of 62 nucleic acids, and the 3' UTR of 513 nucleic acids. The amino acid sequence corresponds to amino acids 1 to 1650 of SEQ ID NO:2.

Please amend the paragraph on page 8, lines 30-31, as follows:

Figures [2 a-c] 2 a-i show a multiple sequence alignment of the amino acid sequence of SEQ ID NO:2 in comparison with known mouse [(SEQ ID NO:4)](SEQ ID NO:5) and human [(SEQ ID NO:3)](SEQ ID NO:4) kinase.

Please amend the paragraph on page 10, lines 2-18, as follows:

In one embodiment, the isolated proteins of the present invention, preferably 14790 proteins, are identified based on the presence of at least one "Ser/Thr kinase site" and at least one "ATP-binding region." As used herein, the term "Ser/Thr kinase site" includes an amino acid sequence of about 200-400 amino acid residues in length, preferably 200-300 amino acid residues in length, and more preferably 250-300 amino acid residues in length, which is conserved in kinases which phosphorylate serine and threonine residues and found in the catalytic domain of Ser/Thr kinases. Preferably, the Ser/Thr kinase site includes the following amino acid consensus sequence X_9-g-X-G-X_4-V-X_{12}-K-X-$_{(10-19)}$-E-X_{66}-h-X_8-h-r-D-X-K-X_2-N-X_{17}-K-X_2-D-f-g-X_{21}-p-X_{13}-w-X_3-g-X_{55}-R-X_{14}-h-X_3 [(SEQ ID NO:5)](SEQ ID NO:6) (where invariant residues are indicated by upper case letters and nearly invariant residues are indicated by lower case letters). The nearly invariant residues are usually found in most Ser/Thr

kinase sites, but can be replaced by other amino acids which, preferably, have similar characteristics. For example, a nearly invariant hydrophobic amino acid in the above amino acid consensus sequence would most likely be replaced by another hydrophobic amino acid. Ser/Thr kinase domains are described in, for example, Levin D.E. *et al.* (1990) Proc. Natl. Acad. Sci. USA 87:8272-76, the contents of which are incorporated herein by reference.

Please amend the paragraph on page 10, lines 19-26, as follows:

As used herein, the term "ATP-binding region" includes an amino acid sequence of about 5-40, preferably 5-25, and more preferably 5-15 amino acid residues in length, present in enzymes which activate their substrates by phosphorylation, and involved in binding adenosine triphosphate (ATP). ATP-binding regions preferably include the following amino acid consensus sequence: G-X-G-X-X-G-X(15-23)-K [(SEQ ID NO:6)](SEQ ID NO:7). ATP-binding regions are described in, for example, Samuel K.P. *et al.* (1987) FEBS Let. 218(1): 81-86, the contents of which are incorporated herein by reference. Amino acid residues 596-604 of kinase comprise an ATP-binding region.

Please amend the paragraph on page 11, lines 26-34, as follows:

The nucleotide sequence of the isolated human kinase cDNA and the predicted amino acid sequence of the human 14790 polypeptide are shown in Figure 1 and in SEQ ID NOs:1 and 2, respectively. [A plasmid containing the nucleotide sequence encoding human kinase was deposited with American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on _____ and assigned Accession Number _____. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made

merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.]

Please amend the paragraph on page 15, line 20 through page 16, line 4, as follows:

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 15, 20, 25, 30 or more nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, or the coding region thereof. In other embodiment, the nucleic acid is at least 30, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1500, 2000, 2500, 3000, 3500, 4000, or 4500 nucleotides in length. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 30%, 40%, 50%, or 60% homologous to each other typically remain hybridized to each other. Preferably, the conditions are such that sequences at least about 70%, more preferably at least about 80%, even more preferably at least about 85% or 90% homologous to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65°C. A more preferred example of stringent hybridization conditions is hybridization in 0.5M sodium [phophate] phosphate, 7% SDS at 65°C , followed by one or more washes in 0.2 X SSC at 65°C. Preferably, an isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequence of SEQ ID NO:1, or the coding region thereof, corresponds to a naturally-occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid

molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (e.g., encodes a natural protein).

Please amend the paragraph on page 62, line 35 through page 63, line 6, as follows:

The sequences of the positive clones were determined and found to contain open reading frames. The nucleotide sequence encoding the human 14790 protein is shown in Figure 1 and is set forth as SEQ ID NO:1. The protein encoded by this nucleic acid comprises about 1650 amino acids and has the amino acid sequence shown in Figure 1 and set forth as SEQ ID NO:2. The coding region (open reading frame) of SEQ ID NO:1 is shown in Figure 1 as the portion of the nucleotide sequence corresponding to the amino acid sequence of SEQ ID NO:2. [The clone comprising the entire coding region of human kinase was deposited with the American Type Culture Collection (ATCC®), 10801 University Boulevard, Manassas, VA 20110-2209, on _____, 1998, and assigned Accession No. _____.]

Please amend the paragraph on page 63, line 18-25, as follows:

14790 mRNA was found to be expressed in human skeletal muscle, brain and liver. TaqMan RT-PCR analysis revealed that 14790 mRNA was found to be upregulated in liver cells which were infected with HBV. Moreover, mRNA expression of 14790 was found to be restricted to hepatocytes of HBV infected livers as seen b[u]y in situ hybridization. 14790 mRNA was also found to be upregulated in HepG2.2.15 cells (HBV positive) compared to HepG2 parent cells (HBV negative). When HepG2.2.15 cells were treated with anti-HBV drug treatment, the upregulation of 14790 mRNA was eliminated. Thus indicating that a modulator of 14790 activity or mRNA may be used to treat infection by HBV.

In the Claims:

1. (Amended) An isolated nucleic acid molecule selected from the group consisting of:

(a) a nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:1; and

(b) a nucleic acid molecule comprising [the coding region] nucleotides 63 to 4991 of the nucleotide sequence set forth in SEQ ID NO:1.

3. (Amended) An isolated nucleic acid molecule [selected from the group consisting of:

(a) a nucleic acid molecule] comprising [the nucleotide sequence contained in the plasmid deposited with ATCC® as Accession Number _____] the nucleotide sequence set forth in SEQ ID NO:1.

4. (Amended) An isolated nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide having kinase activity comprising the amino acid sequence of SEQ ID NO:2, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:1 or [the coding region] nucleotides 63 to 4991 of SEQ ID NO:1 in 0.5M sodium phosphate, 7% SDS at 65°C, followed by one or more washes in 0.2 X SSC at 65°C [under stringent conditions].

5. (Amended) An isolated nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule comprising a nucleotide sequence which is at least [60] 85% homologous to the nucleotide sequence of SEQ ID NO:1 or at least 90% homologous to [the coding region] nucleotides 63 to 4991 of SEQ ID NO:1;

b) a nucleic acid molecule comprising a fragment of at least [200] 3500 nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1 or [the coding region] nucleotides 63 to 4991 of SEQ ID NO:1, or a complement thereof;

c) a nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence at least about [60] 95% homologous to the amino acid sequence of SEQ ID NO:2; and

d) a nucleic acid molecule comprising a fragment of at least 3500 nucleotides which encodes [a fragment of]a polypeptide comprising a fragment of the amino acid sequence of SEQ ID NO:2[, wherein the fragment comprises at least 15 contiguous amino acid residues of the amino acid sequence of SEQ ID NO:2];

wherein the nucleic acid molecule encodes a polypeptide having kinase activity.

Please delete claim 6 without prejudice or disclaimer.

7. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence which is completely complementary to the nucleotide sequence of the nucleic acid molecule of any one of claims 1, 2, 3, 4, or 5.

12. (Amended) A method of producing a polypeptide comprising culturing a host cell transfected with the vector of claim 9 in an appropriate culture medium to, thereby, produce the polypeptide expressed by the nucleic acid molecule.

22. (Amended) A kit comprising a nucleic acid molecule of any one of claims 1, 2, 3, 4, or 5 to a compound [a compound] which selectively hybridizes in 0.5M sodium phosphate, 7% SDS at 65°C, followed by one or more washes in 0.2 X SSC at 65°C, to a compound [a nucleic acid molecule of any one of claims 1, 2, 3, 4, or 5] and instructions for use.

Please delete claims 27, 29-30 without prejudice or disclaimer.